REMARKS

This application relates to a method for measuring the effect of chemical substances on the electrophysiological properties of tissue samples. The effect that is measured is a chronic effect. The device that measures the electrical properties of a tissue sample has multiple electrodes for contacting the sample.

In the outstanding Office Action (Paper No. 31, mailed May 21, 2002), claims 12, 14, and 16 were rejected on various bases. In this Response, Applicants have amended claim 12 to remove redundant language. After entry of this Amendment, claims 12, 14 and 16 will be under consideration.

Double Patenting Rejection

Claims 12, 14, and 16 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,297,025. The claims in this application are a subset of those found in the '025 patent. Nevertheless, although it is possible to infringe the claims in both the application and the patent with a single method, there is no tie between the two in measuring the "chronic" data for a chosen chemical substance. With such a teaching in the claims, the rejection is believed to be ill-founded in law. However, since the term of any patent issuing from this application will terminate when the term of the '025 concludes, Applicants are willing to provide a Terminal Disclaimer to conclude prosecution in a more expeditious manner.

Submitted herewith is a Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c). Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 12, 14, and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Office Action states:

> "Claim 12 is rejected as being vague and not clear. The claim is confusing since the device (i.e., detector comprising) in lines 5-6 is mixed with the method (i.e., contacting, detecting) steps."

Claim 12 is a method claim and has been amended. In particular, the claim has been rewritten to specify that the device to be used in the process is "configured" to have the capability recited there. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 12, 14, and 16 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Yamamoto et al. 1982 (Brain research, 244:382-386). Specifically, the Office Action states:

> "Yamamoto et al. disclose a method of testing the effect of black widow spider venom (chemical substance) pro[illegible]ling contacting the hippocampal tissue sections with glass micropipettes filled with potassium acetate for measuring intracellular potentials (see abstract and page 382). Electrical stimulation was given to the tissue sample (i.e., electrodes on a substrate and electrical properties were measured before and after the addition of venom (figures 1 and 2). Further, the synaptic transmission after prolonged administration (3 days) of venom (page 385, left column first paragraph through right column) is also disclosed."

Applicants disagree. "To anticipate a claim, the reference must teach every element of the claim." MPEP 2131. The claimed process measures the chronic effect of chemical substances on neural or muscle tissue samples, for instance, after a time period of about three days. The process also provides a detector that has a plurality of microelectrodes. The plurality of microelectrodes detects an electrical property of the tissue sample when contacted by the tissue sample.

Yamamoto et al. describe an acute experiment, which at the longest, lasts for 20 minutes (p. 383, right column, line 3). The prolonged administration that the Examiner refers to at p. 385 summarizes the type of administration found in references 3 and 4 of

the bibliography, not the protocol followed by Yamamoto et al. Therefore, the cited reference does not disclose chronic administration nor measurement.

Furthermore, electrical stimulation was delivered using only a single electrode (p. 382, right column, lines 19-22). As such, the element of multiple electrodes has not been satisfied.

Therefore, a rejection under 35 U.S.C. §102(b) is improper and Applicants respectfully request that it be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Gahwiler et al. in view of Gross et al.

Claims 12, 14, and 16 stand rejected under 35 U.S.C. §103(a) as being upatentable over Gahwiler et al. (Neuroscience, 1982, 7; 1243-1256), in view of Gross et al. (J. of Neuroscience Methods 5: 13-22, 1982). Specifically, the Office Action states:

> "Gahwiler et al 1982, teach a method of testing the effect of chemical substances (acetylcholine) on neuronal tissue (hippocampal sections) and measuring the electrical properties (see experimental procedures on page 1243 and 1244) before and after addition of said substances (see results and figures). Although the prior art used standard electrophysiological techniques for recording the electrical properties, the prior art specifically does not teach providing a detector comprising plurality of microelectrodes on a substrate for contacting the tissue sample (i.e., the device or apparatus)."
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> "Gross et al teach an apparatus (see material and methods/figures) for observing a physical and chemical property of a tissue or cells comprising providing photoetched electrodes integrated into the floor of a tissue culture chamber (i.e. providing a substrate with planar electrodes disposed on the same plane as the substrate) and a cell culturing means. (page 13). Gross et al teach recording the electrophysiological potentials with electrodes integrated into the tissue culture plate would allow the long term monitoring of neuronal activity. It would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to us e the apparatus designed by Gross in a method of Gahwiler

et al to measure the electoral properties before and after addition of chemical substances because Gross et al suggests that the apparatus disclosed in obviously designed for long term cultures. The motivation to use this apparatus to achieve the obviously designed for long term cultures. The motivation to use this apparatus to achieve the obvious benefits is clearly suggested by Gross (see page 21, last paragraph). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the apparatus as taught by Gross et al for measuring and comparing waveforms or electrical properties of neural tissue before and after the addition of chemical substances as taught Gahwiler et al because the apparatus is designed to measure the effect of different concentrations of the chemical substance on tissue and comparing the electrical properties of long term cultures."

Applicants disagree. Again, the amended claims recite a method that provides for a device having multiple electrodes. The electrodes measure the chronic effect of a chemical substance on neural or muscle tissue samples.

Although Gahwiler et al. measure the electrical properties of a hippocampal slice exposed to such compounds as acetylcholine and atropine, the measurements are obtained acutely, not after a time period deemed to be chronic. Figure 1 states that the explant had been cultured for 49 days, but this refers to a roller-tube technique used to prepare the hippocampal cultures, not the duration of tissue exposure to the test compound. Therefore, Gahwiler et al. do not measure a chronic effect on tissue samples.

Furthermore, Gross et al. describe a device that cultures mouse spinal tissue cells on a multielectrode plate. The plate records electrophysiological potentials for no longer than 48 hours. The cited reference also teaches measuring electrical properties of cells that are "almost a monolayer" (Fig. 5). As such, there is no teaching of chronic measurement by the device of Gross et al. There is also no suggestion that the device can be used measure electrical properties of neural or muscle tissue samples.

Therefore, Applicants point out that one of skill would not be motivated to use the device of Gross et al. with the method of Gahwiler et al. since the device does not obtain chronic measurements and because it does not record the electrophysiological activity of neural or muscle tissue, only that of clumps of cells. Assuming *arguendo*, that the cited

references were combined, they still would not result in the claimed method. The step of measuring a chronic response of neural or muscle tissue would not be taught, as required by the claims under consideration.

Prima facie obviousness has not been established, and withdrawal of the rejection is respectfully requested.

Gahwiler et al. in view of Gaiver et al.

Claims 12, 14, and 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gahwiler et al. (Neuroscience, 1982, 7; 1243-1256) in view of Gaiver et al. (U.S. Patent 5,187,096). Specifically, the Office Action states:

> "Gaiver et al teach an apparatus (see claims) for observing a physical and chemical property of a tissue or cells comprising plurality of electrodes integrated into the floor of a tissue culture chamber (i.e. providing a substrate with planar electrodes disposed on the same plane as the substrate) and cell culturing (column 2, Summary of the invention) means. Gaiver et al teach by using this apparatus, the activities of cultured cells that are attached to the surfaces could be followed continuously in real time. The recording of extracellular electrophysiological potentials with electrodes integrated into the tissue culture plate would allow the long term monitoring of cell activity to change in the physical environment and drugs (column 3 and 4). It would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to use the apparatus designed by Gaiver et al in a method of Gahwiler et al to measurer the electrical properties before and after the addition of chemical substances because Gaiver et al suggests that this apparatus is obviously designed for long term cultures. The motivation to use this apparatus to achieve the obvious benefits is clearly suggested y Gaiver et al. (see column 3, lines 23-55). therefore it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the apparatus as taught by Gaiver et al for measuring and comparing waveforms or electrical properties of neural tissue before and after the addition of chemical substances as taught by Gahwiler et al because the apparatus designed by Gaiver is fore measuring the effect of different concentration of the chemical

> substances on tissue and comparing the electrical properties of long term cultures."

U.S. Patent 5,187,096 is to Giaever et al., not Gaiver et al. For purposes of this rejection Applicants will assume that the Examiner is citing U.S. Patent 5,187,096 to Giaever et al. and request correction if this is incorrect.

Applicants disagree. The cited reference teaches recording cell potentials only for hours (p. 1244, under "RESULTS"). Thus, as described above, Applicants again point out that Gahwiler et al. does not disclose a method for measuring a chronic response of tissue samples to a chemical substance.

Furthermore, the Examiner is incorrect in characterizing the device taught by Giaever et al. ('096 patent) as an apparatus that records electrophysiological potentials. A closer reading of the '096 patent reveals that the device "can detect and measure the following: cell attachment, cell spreading, lateral motion of cells, porosity, areas involved in adhesion plaques, cell-substrate spacing, and vertical cell motion" (3:26-30). The method is accomplished by measuring changes in the impedance of the electrodes (2:57-64). The disclosure in the body of the '096 patent also clearly identifies what the device is measuring. See column 6, lines 52-55:

> "It is important to understand that the apparatus and method of the present invention detects the activity of cells electrically since the cells effect the impedance measurement."

Therefore, Giaever et al. do not teach a method of measuring the electrical properties of neural or muscle tissue, as required by the claims. The cited reference suggests detecting and measuring activities of cultured cells that relate to cell attachment and cell spreading. Put simply, one of ordinary skill would not be motivated to use a device that does not detect electric potentials in a method that calls for the measurement of electric potentials. Consequently, it is also clear that the combination of Gahwiler et al. with Giaever et al. does not render obvious the rejected claims.

Withdrawal of the rejection is therefore believed to be appropriate.

Gahwiler et al. in view of Sugihara et al.

Claims 12, 14, and 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gahwiler et al. (Neuroscience, 1982, 7; 1243-1256) in view of Sugihara et al. 1995, (EPA: 689051). The Office Action states:

> "Applicant states (see Paper # 22, filed on 4/5/01) that the current application was filed on 9/24/1997. This application is a PCT 371 filed on 1/24/1997, which in turn has priority to Japanese application filed on 1/24/96. The current application also claims priority to U.S. application 08/662,629, filed on 6/13/96, which in turn is a CIP of 08/464,116 filed on 6/5/1995. Examiner has reviewed the application 08/464,116 filed on 6/5/1995 and found no support for the claimed invention, directed to a method of testing the chronic effect on neuronal muscle tissue samples of chemical substance using a detector comprising plurality of microelectrodes on a substrate for contacting the tissue sample and detecting an electrical property of said tissue before and after adding the chemical substance. Therefore, this application does not get priority to 08/464,116 filed on 6/5/1995 and gets priority to U.S. application 08/662,629 filed on 6/13/96. Since this application filed under 35 U.S.C. 119 (a)-(d), the priority date for the pending claims is 1/24/96. Therefore, Sugihara et al. EPA 689051 (12/27/1995) is considered as prior art."
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> "Gahwiler et al 1982 teach a method of testing the effect of chemical substances (acetylcholine) on neuronal tissue (hippocampal sections) and measuring the electrical properties (see experimental procedures on page 1243 and 1244) before and after the addition of said substances (see results and figures. Although the prior art used standard electrophysiological techniques for recording, the prior art specifically does not teach providing a detector comprising plurality of microelectrodes on a substrate for contacting the tissue sample (i.e., the device or apparatus)."
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> "Sugihara et al teach an apparatus for observing physical and chemical property of a tissue or cells comprising plurality electrodes integrated into the floor of a tissue culture chamber (i.e. providing a substrate with planar electrodes disposed on the same plane as the substrate) and a cell culturing means. (Claims). Sugihara et al teach by suing the disclosed apparatus, the activities of cultured cells that are attached to the surface could be followed

> continuously in real time. The recording of extracellular electrophysiological potentials with electrodes integrated into the tissue culture plate would allow the long term monitoring of cells activity to changes in the physical environment and drugs (claims and figures). It would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to use the apparatus as taught by Sugihara et al for measuring and comparing waveforms or electrical properties of neural tissue before and after that addition of chemical substances as taught by Gahwiler et al because the apparatus designed by Sugihara et al is for measuring the effect of different concentrations of chemical substances on tissue and comparing the electrical properties of long term cultures."

Applicants traverse this rejection on the grounds that EPA 689051 ("Sugihara") is not prior art. If an application is a continuation-in-part application, any claims which are fully supported under 35 U.S.C. §112 by the earlier parent application have the effective filing date of that earlier parent application. MPEP 706.02. Therefore, Applicants maintain that the subject application is entitled to the effective filing date of June 5,1995 regarding this rejection.

The history and timing of the various applications and patents of Sugihara et al., including the relationship between this application and EPA 689051 are discussed at length in the Response filed on April 5, 2001, and the Examiner is invited again to review the sequence described there.

The Examiner agrees that Gahwiler et al. do not teach a detector having a plurality of microelectrodes. The disclosure of Sugihara is then used to supply this missing device limitation. However, a detector having a plurality of microelectrodes that contact tissue and that provide long term measurement of electrophysiological potentials is supported throughout the disclosure of U.S. Application No. 08/464,116, now U.S. 5,563,067, for example, at 4:51-57 and 9:57-63. Thus, contrary to the Examiner's conclusion, the subject matter pertaining to a multielectrode detector is entitled to the priority date of June 5, 1995. Accordingly, Sugihara cannot be considered as prior art under 35 U.S.C. §102, and thence under §103.

Withdrawal of the rejection is respectfully requested.

SUMMARY

Applicants have responded to each matter of substance raised in the Office Action and believe the application to be in condition for allowance. Should the Examiner have any questions, comments, or suggestions, he is urged and invited to contact the Applicants' representative at the number listed below. Should an interview be considered desirable, please feel free to also contact Applicants' representative for a personal or telephone interview.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned **"VERSION WITH MARKING TO SHOW CHANGES MADE."**

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned representative so that prosecution may be expedited.

In the unlikely event that the Patent Office determines that an extension and/or other relief is required as a result of this statement, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to our **Deposit account no. 03-1952** referenced Docket No. **356972020100**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: August 21, 2002 By:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

12. (Five Times Amended) A method of testing the chronic effect on neural or muscle tissue samples of chemical substances[, which] compris[es]ing:

providing a detector, wherein the detector compris[ing]es a plurality of microelectrodes on a substrate [for] configured to contact[ing] the tissue sample and [detecting an electrical property of said tissue sample to which a chemical substance has been added and said plurality of microelectrodes further for] apply[ing] an electric stimulus to the tissue sample;

contacting said neural or muscle tissue sample with [a] the plurality of [said] electrodes;

measuring the electrical properties of the neural or muscle tissue sample;

adding said chemical substance to the neural or muscle tissue sample;

measuring the electrical properties of the neural or muscle tissue sample [after said addition of said chemical substance to the neural or muscle tissue sample and] at a time which measures chronic response to said chemical substance; and

comparing said electrical properties before and after said addition of said chemical substance to determine whether said added chemical substance has had an influence on the neural or muscle tissue sample.